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Pharmacological Effects of *Thunbergia laurifolia* Lindl. Extract on Gastric Ulceration in Rats

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Abstract

Thunbergia laurifolia Lindl. (TL), a medicinal plant renowned for its anti-inflammatory properties, has attracted interest in its potential antiulcerogenic effects. Gastric ulcers, typically resulting from an imbalance between aggressive factors such as gastric acid and the protective defenses of the gastric mucosa, are frequently aggravated by inflammatory processes. This study aimed to investigate the anti-ulcerogenic potential of TL extract in animal models. Male Sprague Dawley rats were selected for the study. The anti-ulcerogenic effects were evaluated using four distinct in vivo models: ethanol/hydrochloric acid administration, restraint water immersion stress, indomethacin administration, and pylorus ligation. Administration of TL extract at doses of 100, 200, and 400 mg/kg significantly reduced gastric ulcer formation induced by ethanol/hydrochloric acid as well as restraint water immersion stress. At doses of 200 and 400 mg/kg, the extract significantly reduced indomethacin-induced ulcer formation. Additionally, at a dose of 400 mg/kg, the extract significantly reduced both gastric secretion rate and total acidity in the pylorus ligation model. The findings of this study indicate that TL extract exhibits noteworthy anti-ulcerogenic activity in rats, suggesting its potential therapeutic value in treating gastric ulcers.

Keywords**:** *anti-ulcerogenic activity; Thunbergia laurifolia Lindl; rang jeud; gastric lesion*

1. Introduction

Thunbergia laurifolia Lindl. (TL, Family Acanthaceae), commonly known in Thai as “Rang Jeud”, has been traditionally used for centuries as an antipyretic as well as an antidote for counteracting various poisons, toxins and overdosed drugs (Suksaeree et al., 2023). TL exhibits several pharmacological activities, including decreasing blood glucose level in diabetic rats (Aritajat et al., 2004), anti-mutagenic (Saenphet et al., 2005), hepatoprotective (Pramyothin et al., 2005) and antioxidant activities (Chan, & Lim, 2006; Sunthrarak, & Oonsrivilai, 2022). Recent research highlights its potential in treating neurodegenerative conditions such as Alzheimer's disease. TL leaf extracts protect against beta-amyloid-induced neurotoxicity, reducing reactive oxygen species (ROS) and enhancing antioxidant enzyme activities and cell survival in neuronal models (Homwuttiwong et al., 2024). The leaf extracts demonstrate high total phenolic content, which correlates with strong antioxidant activity and have been shown to cause no significant acute or sub-chronic toxicity (Posridee et al., 2022). This suggests a

safe profile for consumption and making it a candidate for therapeutic applications.

The pharmacological studies of TL have extended beyond its traditional use in Thai medicine, highlighting its multifaceted medicinal value. Thus, our study aims to focus on the protective effect of TL in the models of peptic ulcer. It has been shown in a previous study conducted in a mouse model that TL possessed anti-nociceptive and anti-inflammatory activities (Boonyarikpunchai et al., 2014; Aiamsa-ard et al., 2024). Because of the significant protective mechanisms against peptic ulcers, primarily rely on antioxidant properties and cytoprotective effects, we hypothesize that TL might enhance gastric mucosal defense and reduce oxidative stress, which are critical in ulcer prevention and treatment. Thus, this study evaluated the plant's total phenolic content, which correlates positively with its antioxidant activity and explored its modulation of inflammatory responses in several peptic ulcer models. Additionally, the experiments measured gastric acid secretion and healing of gastric lesions, further supporting its protective role against ulcers.

2. Objectives

The present study aimed to assess the protective effect of TL extract against gastric ulcers using various *in vivo* models.

3. Materials and Methods

3.1 Animal and Ethical Considerations

Male Sprague Dawley (SD) rats, weighing between 250 and 300 grams, were supplied by the National Laboratory Animal Center in Nakhon Pathom, Thailand. These rats were housed in a controlled environment with a stable temperature of 25±1°C and a 12-hour light-dark cycle. To ensure proper acclimatization, the rats were provided with a standard diet and water ad libitum for one week before the experiments commenced. The study protocols received approval from the Animal Ethics Committee of the Faculty of Medicine at Thammasat University (AE013/2014).

3.2 Preparation of *Thunbergia laurifolia* Lindl. (TL) Water Extract

Briefly, TL leaves were boiled in water for 1 h and filtered. A spray drying process was then carried out. Quality control of the dry extract, including physical appearance, percentage of loss on drying, and quantity of chemical compounds (total phenolic content, total flavonoid content, percentage of caffeic acid, and percentage of rosmarinic acid) was performed according to Thai Herbal Pharmacopoeia.

3.3 Preparation of Rats for Anti-ulcerogenic Activity Study

Male rats (n=6 per group) were assigned to different experimental groups. Prior to the experiment, all animals underwent a 48-hour fasting period with free access to water, which was withdrawn one hour before the initiation of the study. The control group received an oral administration of distilled water, while the positive control group was given cimetidine at a dose of 100 mg/kg. The experimental groups were treated with TL extract at doses of 100, 200, and 400 mg/kg, administered orally. All treatments were provided one hour prior to the induction of gastric lesions. All procedures were conducted in accordance with ethical guidelines and institutional animal care standards.

3.4 Test Substance Administration

Test substances were administered orally using distilled water as the vehicle. TL extract was given at doses of 100, 200, and 400 mg/kg body weight, and cimetidine at 100 mg/kg body weight, each in a volume of 5 mL/kg. The solutions were prepared by dissolving or suspending the substances in distilled water. Administration was performed via oral gavage to ensure precise dosing, with animals being weighed beforehand to calculate the exact volume needed. Control groups received the same volume of distilled water. Post-administration, animals were monitored for reactions and subsequently assessed according to the experimental objectives.

3.5 Ethanol/Hydrochloric Acid (EtOH/HCl)-Induced Gastric Lesions

According to the method previously described by Mizui, & Doteuchi (1983), 1 mL of an EtOH/HCl solution composed of 60 mL absolute ethanol, 1.7 mL concentrated hydrochloric acid, and 38.3 mL distilled water was administered orally to each rat using a gastric gavage needle. After a one-hour period, during which the rats were kept in their cages under standard conditions, they were humanely euthanized and sacrificed. The stomachs were then carefully excised and examined for lesions. To assess the extent of gastric damage, the stomachs were opened along the greater curvature, and lesions were documented and scored based on size, number, and severity.

3.6 Restraint Water Immersion Stress-induced Gastric Lesions

To induce gastric lesions using restraint water immersion stress, rats are placed in stainless steel cages and immersed up to their xiphoid in a water bath at 20 ± 2°C for five hours, following the method by Takagi et al., (1964). After immersion, the rats are euthanized, and their stomachs are removed and examined for lesions. The lesions are assessed based on their number, size, and severity, with histo-pathological analysis available for detailed tissue examination. A control group that was not subjected to the procedure was included for comparative analysis.

3.7 Indomethacin-Induced Gastric Lesions

To induce gastric lesions in rats, a suspension of indomethacin in 5% Tween 80 was prepared and administered intraperitoneally at a dose of 30 mg/kg, as outlined by Djahanguiri (1969) and Hayden et al., (1978). The preparation of the indomethacin suspension involves dissolving the appropriate amount of indomethacin in 5% Tween 80, which acts as an emulsifier to ensure the drug is evenly distributed in the solution. The mixture should be prepared fresh and well-shaken to achieve a homogeneous suspension. Each rat receives 30 mg/kg of indomethacin by intraperitoneal injection, which required careful handling to avoid any undue stress or injury to the animal. After administering the drug, the rats are monitored for five hours to allow sufficient time for the drug to induce gastric lesions. Following this period, the rats are humanely euthanized using a method compliant with ethical standards. Once euthanized, the rats' stomachs are carefully excised for examination. The gastric mucosa is assessed for lesions by opening the stomach along the greater curvature and systematically evaluating the extent, size, and severity of the lesions.

3.8 Pylorus Ligation

Pylorus ligation was carried out following the method outlined by Shay et al., (1945). One hour after administering the test substance, rats were lightly anesthetized with ether. The abdomen was surgically opened, the pylorus was ligated, and the abdomen was then sutured closed. Five hours later, the animals were euthanized with an overdose of ether. The stomach was excised, and its contents were analyzed for volume, pH, and total acid output. The gastric juice was centrifuged, and the acidity of the supernatant was determined by titration with 0.1 N NaOH to a pH endpoint of 7.4, using phenolphthalein as an indicator. Results were expressed as milliliters and microequivalents per 100 g body weight per hour.

3.9 Evaluation of Gastric Lesions

Following euthanasia, the stomach was carefully excised from each rat and prepared for detailed examination of gastric lesions. The excised stomach was first opened along with the greater curvature to allow full access to the mucosal surface. After opening, the stomach was thoroughly rinsed with isotonic saline to remove any residual blood or debris, ensuring a clear view of the lesions. The stomach was then pinned onto a wax plate or board to keep it flat and stabilized during examination. The glandular portion of the stomach, which is the primary site for ulcer formation, was systematically inspected under a dissecting microscope with 10X magnification to identify and document the lesions.

To quantify the lesions, the lengths of each visible lesion were measured in millimeters using the dissecting microscope's calibrated micrometer scale. This precise measurement allows for a detailed assessment of lesion size and distribution. The ulcer index for each rat was calculated by summing the total length of all lesions observed in that individual, then averaging this value across all rats in the group to determine the group mean ulcer index.

3.10 Statistical Analysis

Data were expressed as mean ± standard error of the mean (S.E.M.). Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test was applied to assess normality. For normally distributed data, one-way analysis of variance (ANOVA) was used, followed by Tukey's multiple comparison test. For non-normally distributed data, the Kruskal–Wallis nonparametric ANOVA was employed, followed by Dunn's post hoc test. A p-value of less than 0.05 was considered statistically significant.

4. Results

4.1 Characteristics of TL Extract

TL extract was analyzed as previously reported (Nanna et al., 2017). The substance appears as a brown powder and exhibits a 5.98% loss on drying. Its total phenolic content is measured at 18.51% gallic acid equivalent (GAE), while the total flavonoid content stands at 3.29% quercetin equivalent (QAE). The material is freely soluble in water and slightly soluble in 95% ethanol. Additionally, High-performance liquid

chromatography (HPLC) analysis reveals that it contains 0.14% caffeic acid and 0.24% rosmarinic acid.

4.2 Anti-ulcerogenic Activity of TL Extract

The anti-ulcerogenic activity of TL extract was assessed using various gastric ulcer models, including ethanol/hydrochloric acid (EtOH/HCl) administration, restraint water immersion stress, indomethacin administration, and pylorus ligation.

In the EtOH/HCl-induced gastric lesion model, TL extract at doses of 100, 200, and 400 mg/kg, as well as cimetidine at 100 mg/kg, significantly reduced gastric lesion formation compared to the control group ($p<0.05$), as detailed in Table 1. Notably, TL extract at 400 mg/kg demonstrated a greater reduction in gastric lesions than cimetidine (100 mg/kg), though this difference was not statistically significant.

Similarly, in the restraint water immersion stress model, TL extract at 100, 200, and 400 mg/kg and cimetidine at 100 mg/kg significantly decreased gastric lesion formation relative to the control group ($p<0.05$) (Table 2).

Table 3 presents the effects of TL extract in the indomethacin-induced gastric lesion model. TL extract at 200 and 400 mg/kg, along with cimetidine at 100 mg/kg, significantly reduced the formation of gastric lesions compared to the control group ($p<0.05$).

In the pylorus ligation model (Table 4), four parameters gastric volume, secretory rate, pH, and total acidity were measured. Cimetidine (100 mg/kg) significantly decreased all these parameters compared to the control group ($p<0.05$). TL extract did not show significant changes in mean gastric juice volume and pH at any dose. However, TL extract at 400 mg/kg significantly reduced the secretory rate and total acidity compared to the control group, whereas TL extract at 100 and 200 mg/kg did not show significant effects.

Table 1 Effects of TL extract and cimetidine on EtOH/HCl-induced gastric lesions in rats

Group	Dose (mg/kg)	Ulcer Index	%Inhibition
Control	-	106.75 ± 6.24	-
Cimetidine	100	24.08 ± 4.19*	77.44
TL extract	100	84.33 ± 1.63*	21.00
	200	40.62 ± 6.39*	61.95
	400	19.55 ± 6.23*	81.69

Values are expressed as mean ± S.E.M. (n=6)

* Significantly different from the control group (distilled water), $P<0.05$

Table 2 Effects of TL extract and cimetidine on restraint water immersion stress-induced gastric lesions in rats

Group	Dose (mg/kg)	Ulcer Index	%Inhibition
Control	-	9.67 ± 0.81	-
Cimetidine	100	1.88 ± 0.12*	80.52
TL extract	100	6.22 ± 0.36*	35.69
	200	4.45 ± 0.67*	53.97
	400	2.28 ± 0.37*	76.38

Values are expressed as mean ± S.E.M. (n=6)

* Significantly different from the control group (distilled water), $P<0.05$

Table 3 Effects of TL extract and cimetidine on indomethacin-induced gastric lesions in rats

Group	Dose (mg/kg)	Ulcer Index	%Inhibition
Control	-	5.10 ± 1.09	-
Cimetidine	100	1.10 ± 0.11*	78.43
TL extract	100	3.25 ± 0.68	36.27
	200	2.75 ± 0.70*	46.08
	400	1.43 ± 0.21*	71.90

Values are expressed as mean ± S.E.M. (n=6)

* Significantly different from the control group (distilled water), $P<0.05$

Table 4 Effects of TL water extract and cimetidine in pylorus ligation model

Group	Dose (mg/kg)	Gastric volume (mL)	Secretory rate (mL/100g/5h)	pH	Total acidity (mEq/100g/5h)
Control		4.70 ± 0.37	0.43 ± 0.04	1.56 ± 0.19	55.76 ± 4.66
Cimetidine	100	1.68 ± 0.23*	0.16 ± 0.02*	3.78 ± 0.81*	11.26 ± 1.46*
TL extract	100	5.55 ± 0.52	0.49 ± 0.03	1.48 ± 0.02	56.30 ± 1.68
	200	4.70 ± 0.41	0.42 ± 0.03	1.41 ± 0.03	52.23 ± 4.61
	400	3.77 ± 0.40	0.34 ± 0.03*	1.56 ± 0.06	38.29 ± 3.90*

Values are expressed as mean ± S.E.M. (n=6)

* Significantly different from the control group (distilled water), $P<0.05$

5. Discussion

Medicinal plants have long been recognized for their therapeutic potential, particularly in the management of peptic ulcers, which are characterized by the erosion of the stomach lining due to factors like *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (Adebodun et al., 2023; Yadav et al., 2024). These ulcers affect a significant portion of the global population, prompting a search for effective treatments that minimize side effects associated with conventional medications (Nivetha et al., 2023). This study identified the potential use of TL extract in the protection of peptic ulcers using various rat models of gastric ulceration. TL possesses high phenolic and flavonoid compounds, which suggest anti-inflammatory and antioxidant properties. This study utilized four distinct in vivo models to explore the anti-ulcerogenic potential of TL extract: EtOH/HCl administration, restraint water immersion stress, indomethacin administration, and pylorus ligation. TL exhibits protective mechanisms in peptic ulcers by lowering ulcer index, gastric secretory rate, and total acidity.

Peptic ulcer models in rats are crucial for understanding ulcer pathophysiology and testing therapeutic agents. Notable models include the ethanol/ hydrochloric acid (EtOH/HCl), restraint water immersion stress, and indomethacin-induced ulcers, each with distinct mechanisms and implications for research. In ethanol/HCl model, gastric ulcers are induced by the administration of ethanol and HCl, leading to mucosal damage and inflammation. It is widely used to study the protective effects of various compounds against ulcer formation (Satapathy et al., 2024). In contrast, restraint water immersion stress model simulates stress-induced ulcers by subjecting rats to physical restraint and water immersion, which triggers gastric mucosal injury due to increased gastric acid secretion and reduced blood flow (Singh et al., 2022). The indomethacin model utilizes indomethacin, an NSAID, which is known to cause gastric ulcers by inhibiting prostaglandin synthesis, leading to increased gastric acid secretion and mucosal damage. In addition, the pylorus ligation model induces gastric ulcers by ligating the pylorus, leading to increased gastric acid secretion and ulcer formation. This model is widely used due to its reproducibility and ability to mimic human gastric ulcers (Satapathy et al., 2024). While these models provide valuable insights into ulcer mechanisms and potential treatments, they also highlight the complexity of ulcer pathogenesis, necessitating further research to refine therapeutic strategies.

Examples of medicinal plants with gastroprotective properties include Aloe vera, ginger, and turmeric. These plants exhibit anti-inflammatory and mucoprotective effects, which contribute to the healing of ulcers. (Tiwari et al., 2023; Nivetha et al., 2023). These plants may lower gastric acidity, enhance mucosal defense, and possess antioxidant properties, contributing to their therapeutic efficacy (Adebodun et al., 2023; Shahzad et al., 2024). TL has been previously documented for its anti-nociceptive and anti-inflammatory properties which may potentially exert its gastroprotective effect (Boonyarikpunchai et al., 2014; Nanna et al., 2017). This study employed cimetidine as a reference compound to compare anti-ulcer effects. Cimetidine is a histamine 2 (H2) receptor antagonist that is essential for alleviating peptic ulcers by reducing gastric acid secretion, thereby offering mucosal protection. It selectively blocks H2 receptors on parietal cells, resulting in decreased acid production and facilitating the healing of the gastric mucosa (Singh et al., 2018).

TL extract protected against EtOH/HCl-induced ulcers by counteracting the necrotic effects of ethanol and hydrochloric acid on gastric mucosa. This protection may occur through mechanisms such as increased gastric mucus production, enhanced prostaglandin levels, preservation of endogenous glutathione, and improved gastric mucosal blood flow (Miller, & Henagan, 1984; Miyata et al., 1991). The

H2 receptor antagonist cimetidine could mitigate these lesions by suppressing acid secretion, thereby providing mucosal protection (Miyata et al., 1991). Consequently, the EtOH/HCl model is commonly used to assess agents that enhance gastric mucosal protection. The water immersion model represents acute stress ulcers in rats. TL extract could diminish ulcer formation in this model by decreasing acid secretion and/or increasing gastric mucosal blood flow (Kitagawa et al., 1979), reducing gastric motility (Garrick et al., 1986), and enhanced alkaline secretion (Takeuchi et al., 1990). In the third model of gastric ulceration, TL may inhibit indomethacin-induced peptic ulcer through the blockade of gastric mucosal barrier disruption by COX-1, leading to increased prostaglandin synthesis and contributing to ulcer prevention (Hawkins, & Hanks, 2000). Lastly, in the pylorus ligation model, gastric acid hypersecretion plays a pivotal role in ulcer formation. Pylorus ligation leads to gastric acid accumulation, resulting in auto-digestion of the mucosa and disruption of the mucosal barrier (Sairam et al., 2002). TL extract showed anti-secretory activity. TL extract at a dose of 400 mg/kg significantly reduced both the secretory rate and total acidity of gastric juice, indicating that the anti-ulcerogenic effect is likely due to its anti-secretory properties. Despite its promising pharmacological activities, further studies are necessary to fully elucidate the mechanisms underlying these effects and to explore their potential in clinical applications. The integration of herbal medicines with conventional treatments reveals favorable outcomes. For example, combining herbal remedies with standard treatments can enhance therapeutic outcomes and improve patient quality of life (Tiwari et al., 2024). Monitoring for potential herb-drug interactions is crucial to ensure safe integration of these therapies (Tiwari et al., 2024).

6. Conclusion

In summary, TL extract significantly reduced the ulcer index in rat models of gastric ulceration induced by EtOH/HCl, restraint water immersion stress, and indomethacin. At the high dose of 400 mg/kg, TL extract also notably decreased gastric acid secretion rate and total acidity of gastric juice. These results suggest that the anti-ulcerogenic activity of TL extract is likely due to its ability to inhibit gastric secretion and/or enhance protective factors. While TL extract offers promising alternatives for peptic ulcer management, further research is essential to validate their efficacy and safety in clinical settings.

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